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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Charles E. ROGLER et al.

Serial No.: 09/344,189 Art Unit: 1632

Filed: June 24, 1999 Examiner: P. Paras, Jr.

For: **CHRONIC HEPATITIS VIRUS INFECTION AND CLONAL HEPATO-CELLULAR CARCINOMA IN MOUSE REPOPULATED LIVERS**

DECLARATION OF PROFESSOR CHARLES E. ROGLER UNDER 37 C.F.R. § 1.132

1. I, Charles E. Rogler, am Professor of Medicine and Microbiology/Immunology at the Albert Einstein College of Medicine of Yeshiva University and I am a co-inventor of the above-referenced application.

2. It is my understanding that Examiner has rejected the claims of the subject application as anticipated by Kaye et al., U.S. Patent No. 5,980,886 ("the '886 Patent). It is further my understanding that the rejection is based on the '886 Patent's alleged disclosure of an immunetolerant chimeric mouse with liver degenerated by expression of a non-secreted

urokinase plasminogen activator (uPA) that has been repopulated with human hepatocytes. It is my understanding that the Examiner alleges the disclosure the '886 Patent provides enough information to allow a person of ordinary skill in field of the application to make such a chimeric mouse.

3. I disagree with the Examiner's contention that one of ordinary skill in the art could have made an immunetolerant chimeric mouse with liver degenerated by expression of non-secreted uPA that has been repopulated with human hepatocytes, based on the disclosure of the '886 Patent and the state of the art when that patent application was filed.

4. I have spoken with Dr. Mark Kay, co-inventor of the '886 Patent, on two separate occasions, regarding attempts in his laboratory to make the immunetolerant chimeric mouse with liver degenerated by expression of non-secreted uPA that has been repopulated with human hepatocytes that is described in the '886 Patent. My first discussion with Dr. Kay took place after the receipt of the Office Action that issued on June 7, 2001 but before the filing of the response to that Office Action, on September 7, 2001. My second discussion with Dr. Kay took place after receipt of the Office Action that issued on November 23, 2001. This second discussion took place on or about January 3, 2002. On both occasions that I spoke with Dr. Kay, he informed me that his laboratory had attempted to make the chimeric mouse with degenerated liver repopulated with human hepatocytes that is described in the '886 Patent, but that these attempts had failed.

5. In particular, in the discussion that took place on or about January 3, 2002, Dr. Kay and I discussed the utility of the chimeric immunetolerant mouse that is described in the subject patent application for testing antiviral agents against human hepatitis virus infections. I informed Dr. Kay that the Examiner of the subject application had cited the '886 Patent against

the claims of the application. I explained that the Examiner cited the section of the '886 Patent suggesting that it should be possible to make a transgenic mouse that expresses non-secreted uPA in the liver and mate it with a SCID mouse for the purpose of transplanting human hepatocytes and testing antiviral agents against hepatitis viruses. I further asked Dr. Kay if he had attempted to transplant human hepatocytes into the mice described in the '886 Patent.

6. In response, Dr. Kay informed me that his laboratory had made such mice, and had attempted to transplant human hepatocytes into the mice. Dr. Kay informed me, however, that these attempts were unsuccessful. Dr. Kay informed me that his laboratory had not obtained evidence for successful engraftment of human hepatocytes in the liver of the host immune tolerant chimeric mouse. Hence, the disclosure in the '886 Patent was not enabling for the immune chimeric mouse described therein, even for a laboratory with extraordinary skill in the art of liver regeneration and transplantation, such as Dr. Kay's laboratory.

7. Dr. Joerg Petersen, co-inventor of the subject application, and I, along with our co-authors, published our description of the uPA/RAG-2 mouse with degenerated liver repopulated with human hepatocytes in April 2001 (Petersen et al., *Hepatology* 33, 981-988, 2001; *"Petersen"*).

8. I am not aware of any published or unpublished reports describing creation of a chimeric immunetolerant mouse with degenerated liver repopulated with human hepatocytes that pre-dates *Petersen*. I am aware of one paper describing creation of a chimeric immunetolerant mouse with degenerated liver repopulated with human hepatocytes that was published following *Petersen* (Mercer et al., *Nature Med.* 7, 927-933, 2001, enclosed).

9. Accordingly, to my knowledge, a period of over six years passed from the December 14, 1994 earliest priority date of the '886 Patent until the publication of Mercer et al.

in 2001, before anyone other than the present inventors reported success in constructing a chimeric immunetolerant mouse with degenerated liver that is repopulated with human hepatocytes.

10. I further declare that all statements herein of my knowledge are true and that all statements made on information and belief are believed to be true; and further that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the present application or any patent issuing thereon.

Dated : 5/23/02

Signed: Charles E. Rogler

Charles E. Rogler